with maternal smoking being not significant. Similarly, Tainio et al. (1988) gave relative risks of 1.9 (95% C.I. 1.1, 3.2) for day-care attendance and 2.1 (95% C.I. 1.3, 3.3) for crowding, with ETS exposure again being not significant.

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3.5. Sudden Infant Death Syndrome

Sudden infant death syndrome (SIDS) accounts for about 40% of all postneonatal infant mortality in developed countries (Hoffman & Hillman, 1992). The most recent definition of SIDS and the one currently in use in scientific research in the United States is "The sudden death of an infant under 1 year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" (Hoffman & Hillman, 1992).

Risk factors for SIDS include low birthweight (less than 2500 grams) of infant (Li & Daling, 1991; Malloy et al., 1988; Mitchell et al., 1991; Nicholl & O'Cathain, 1989; Rintahaka & Hirvonen, 1986; Schoendorf & Kiely, 1992; Steele & Langworth, 1966), maternal smoking (Bergman & Wiesner, 1976; Haglund & Cnattingius, 1990; Li & Daling, 1991; Malloy et al., 1992; Mitchell et al., 1992; Mitchell et al., 1993b; Rintahaka & Hirvonen, 1986; Schoendorf & Kiely, 1992; Scragg et al., 1993; Steele & Langworth, 1966), mother young (less than 20 years old) (Haglund & Cnattingius, 1990; Mitchell et al., 1992; Naeye et al., 1976; Rintahaka & Hirvonen, 1986; Steele & Langworth, 1966), unmarried (Li & Daling, 1991; Mitchell et al., 1992), of low socioeconomic status (Mitchell et al., 1992; Rintahaka & Hirvonen, 1986), with high parity (Haglund & Cnattingius, 1990; Li & Daling, 1991), not breastfeeding (Mitchell et al., 1992; Mitchell et al., 1993b; Steele & Langworth, 1966) and with few prenatal clinic visits (Li & Daling, 1991; Rintahaka & Hirvonen, 1986; Steele & Langworth, 1966), infant male (Haglund & Cnattingius, 1990; Naeye et al., 1976), sleeping prone (Fleming et al., 1990; Mitchell et al., 1992; Ponsonby et al., 1993), bed sharing (Mitchell et al., 1992; Scragg et al., 1993) and overheating (Fleming et al., 1990; Ponsonby et al., 1993) and smoking by household members other than the infant's mother (Mitchell et al., 1993b).

SIDS rates have been shown to vary with race/ethnicity (Bulterys, 1990; Irwin et al., 1992; Mitchell et al., 1993a; VandenBerg, 1985), season of the year (Anderson et al., 1993; Mitchell et al., 1991) and geographical area (Anderson et al., 1993; Mitchell et al., 1991). Several substantial studies have failed to detect an association between SIDS and some of the above risk factors; for example, low birthweight of infant (Bartholomew et al., 1987), maternal smoking (Bartholomew

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et al., 1987; Wierenga et al., 1990) and smoking by household members other than the infant's mother (Schoendorf & Kiely, 1992).

Some factors which have been investigated but shown not to be significant risk factors for SIDS include vaccination of infants (Byard, 1991; Sivan et al., 1992), genetic traits (Shannon & Kelly, 1982) and infections (Fleming et al., 1992; Rintahaka & Hirvonen, 1986). Respiratory and gastro-intestinal infections are common in infants and, in SIDS, cases may be contributory factors in the death, but not causal (Byard, 1994).

Maternal smoking usually has an estimated odds ratio (OR) for SIDS of about 2 (Haglund, 1993; Malloy et al., 1988; Mitchell et al., 1993b; VandenBerg, 1985), but typically is not the risk factor with largest OR for SIDS. Two examples of ordered OR's are: i) from VandenBerg (1985), low birthweight (OR= 2.5), maternal smoking (OR= 2.1), mother Maori (OR=2.0) and ii) from Mitchell et al. (1992), infant sleeping prone (OR=4.8), bed sharing (OR= 2.0), mother not breastfeeding (OR=1.9), maternal smoking (OR= 1.8).

In addition to having been shown to be significant risk factors for SIDS, maternal smoking during pregnancy and low birthweight of infants have repeatedly been shown to be associated (Haglund & Cnattingius, 1990; Hoffman et al., 1988; Li & Daling, 1991; Malloy et al., 1988; Mitchell et al., 1993a; Rintahaka & Hirvonen, 1986; VandenBerg, 1985). However, some studies failed to detect an association between the two risk factors and were unable to establish that either was a significant risk factor for SIDS (see, for example, Bartholomew et al., 1987). Several studies have indicated that maternal smoking during pregnancy persisted as a significant risk factor for SIDS after birthweight had been taken into account (Haglund & Cnattingius, 1990; Malloy et al., 1988; Mitchell et al., 1991; Mitchell et al., 1992).

Schoendorf and Kiely (1992) reported a significantly increased risk for SIDS from passive smoking after birth and an even greater risk if the mother smoked both during and after pregnancy.

Haglund and Cnattingius (1990) observed that infants born to women who smoked during pregnancy died earlier with SIDS than infants of nonsmokers. However, this observation was not confirmed by either of two large US studies (Hoffman et al., 1988; Malloy et al., 1992).

Several studies have concluded that a dose-response relationship exists between maternal smoking and the risk of SIDS (Haglund & Cnattingius, 1990; Malloy et

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al., 1992; Mitchell et al., 1992), though a substantial US study (Hoffman, et al., 1988), while observing significantly elevated risks for SIDS in infants of smoking mothers, failed to detect a dose-response relationship. Despite some conclusions which hint at a causal link (Mitchell et al., 1992; Mitchell et al., 1993a), a causal relationship has not been established between SIDS and either maternal smoking during pregnancy or after the birth.

Theories about causes of SIDS include defective respiratory function (Byard, 1991; Milerad & Sundell, 1993), while there are conflicting views about a possible cardiac cause for SIDS (Byard, 1991; Keens, 1990). Airway obstruction due to anatomical or physiological defects resulting in obstructive apnoea has been suggested as a possible mechanism of SIDS (Byard, 1991). A study by Nicholl and O'Cathain (1989) concluded that there are a number of different causes of SIDS and that these causes have different distributions for age at death associated with them. The recent dramatic reduction in the SIDS rate in Australia has been attributed to mothers heeding the advice not to put babies to sleep in the prone position (Ponsonby et al., 1993).

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3.6. CONCLUSION

The effects of ETS on the health of children is difficult to separate from confounders such as age, family history, genetic predisposition, living conditions, smoking during pregnancy and breastfeeding. The multifactorial nature of the illnesses and the general nature of many of the symptoms complicates interpretation of the data. An assessment of published results is particularly complicated due to: the variety of outcomes measured for a given illness, data often being derived from parental self-administered questionnaires requiring parents to recall past illnesses and symptoms in children, and the effects of confounders mentioned above. For infants, particularly those under two years of age, there would appear to be a small increased risk of lower respiratory illness or symptoms, allowing for confounders. For older children, however, generally the risk dissipates with age or disappears altogether.

The changes in lung function associated with ETS are small and not consistent; further, the clinical significance of such observed small reductions in lung function has not been addressed. The effects of ETS on the lung function of children require further investigation.

The studies dealing with upper respiratory infection exhibit inconsistent and inconclusive results. ETS, if it has a deleterious effect at all, results in only a small increase in risk, and is not the only risk factor and likely not the most important.

An association between exposure to ETS and SIDS has been observed, but there are a number of other risk factors for SIDS which appear to be more important. The most prominent of these are: prone sleeping position, low birthweight, maternal smoking during pregnancy and low socioeconomic status of the mother.

Very few studies have adequately accounted for the effects of mother's smoking during pregnancy; those which have show that this is a major and occasionally the only significant factor influencing respiratory illness (lower and upper) and lung function.

4. EFFECT OF ETS ON ADULT HEALTH

4.1. PASSIVE SMOKING AND NON-MALIGNANT RESPIRATORY DISEASES

4.1.1 HEALTHY SUBJECTS

Active smoking alters pulmonary function in susceptible individuals by at least two independent mechanisms:

(i) by progressive narrowing of predominantly peripheral air passages leading to chronic airflow limitation and

(ii) enlargement of alveolar air spaces with eventual destruction or loss of the walls of alveolae leading to a loss of surface area available for gas exchange (emphysema).

On average, smokers have an accelerated loss of function compared with healthy non-smokers, but the rates of decline are highly variable suggesting that not all smokers are susceptible (Fletcher & Peto, 1978). Both cross-sectional and longitudinal studies indicate that the mean annual rate of decline of lung function for smokers increases with amount smoked, but the difference in slope between smokers of 10 cigarettes daily or fewer and non-smokers is small (Peat, Woolcock & Cullen, 1990). Approximately 15% of smokers develop disabling chronic airflow limitation within their lifetime (Fletcher & Peto, 1978; for review see Report of the Surgeon General, 1986). However, Peat and coworkers (1990) reported from the Busselton survey, Western Australia, that 24% of male smokers and 18% of female smokers had chronic airflow limitation (defined as FEV_1 less than 65% predicted) compared with 5% and 8% for male and female non-smokers (presumably asthmatic).

Given that cigarette smoking is accepted as a major cause of pulmonary impairment in otherwise healthy individuals, a number of authorities expressed concern that exposure to environmental tobacco smoke (ETS) might also be injurious to the pulmonary function of the general population. Any such effect would be expected to be very small in population studies based on the limited

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"dose" response data available in the literature. However, it has been argued that some subjects may be especially susceptible through some form of inherited or acquired predisposition. Asthmatics are known to be sensitive to a wide range of environmental exposures and have been regarded as a group at special risk. Studies relevant to asthmatics are reviewed in Section 4.1.2.

In this section experimental studies of the effects of acute exposure to ETS on healthy subjects are reviewed. A review of epidemiological studies of possible long-term effects of exposure to ETS follows.

Acute exposure and lung function

The first detailed study of the effects of acute exposure to ETS appears to have been performed by Pimm, Silverman and Shephard (1978) and is often quoted as showing a small deleterious effect (e.g. NH & MRC, 1986). Twenty healthy young volunteers (lifetime non-smokers) were exposed in an environmental chamber for 2 hours to ETS "comparable to that encountered in rooms heavily polluted with smoke" (carbon monoxide [CO] concentration 24 ppm, particulates > 4 mg/m^3). Most subjects found the experience unpleasant. Measurements of spirometry were performed every 30 minutes during exposure and for 1 hour after exposure (i.e. 7 tests, with 4 variables reported). Lung volumes were measured 3 times (4 variables). Males and females were analysed separately. Although 80 paired t-tests were performed, a significance level of 0.05 was used.

There was no change in FEV_1, FVC or forced expiratory flow at 50% of VC (FEF 50) in either group. In both groups 1 out of 7 of the measurements of forced expiratory flow at 25% vital capacity (FEF 25) showed a significant decline at the 0.05 level (at 90 minutes exposure in males and at 60 minutes post-exposure in the females). If an appropriate correction for the number of t-tests had been used, these changes would have been disregarded as due to chance.

More recently a number of groups have conducted similar experiments comparing the responses of asthmatics and healthy non-smokers (Dahms et al., 1981; Menon et al., 1992; Magnussen et al., 1992; Jörres & Magnussen, 1992; Danuser et al., 1993). With the use of appropriate statistical methods these studies have shown no significant effects on airway function in control subjects and variable effects in asthmatic subjects (see Section 4.1.2 for details).

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Conclusion

Although there is reasonable evidence in the literature that *active* smoking of just 1 cigarette can produce changes in airway resistance (e.g. Nadel & Comroe, 1961), there is no evidence that acute exposure to high levels of ETS for periods of up to 2 hours causes a detectable change in airway function in healthy subjects (for asthmatics see Section 4.1.2).

Chronic exposure and lung function

The evolution of chronic airflow limitation in susceptible active smokers typically takes 20-40 years. Thus it is reasonable to postulate that chronic exposure to ETS might result in some impairment of pulmonary function in extremely susceptible individuals. Asthmatics are considered separately in Section 4.1.2. The other subgroup potentially at risk comprises those with an inherited deficiency of alpha-1-antiprotease, an enzyme which degrades other enzymes responsible for digesting elastin thereby protecting the lung from excessive damage during inflammatory processes. Such individuals develop disabling emphysema and airflow obstruction prematurely if they are active smokers but non-smokers may reach a normal life-expectancy without significant pulmonary disability. The prevalence of this condition in the community is so low that studies of the possible effects of passive smoking have not been attempted.

A number of studies of varied design have been conducted in an attempt to address the question of whether prolonged exposure to ETS can result in pulmonary impairment in otherwise healthy individuals. The results and conclusions have been conflicting and the reported effects have been small and inconsistent. Much has been written about limitations in study design and methodology. Major problems have included reporting bias of smoking status and failure to account for significant confounding factors. A number of reviews of this literature has appeared over the years and all have concluded that the effects, if any, are small and unlikely to be of clinical significance in otherwise healthy individuals (e.g. Weiss et al., 1983; U.S. Surgeon General, 1984 & 1986; NH & MRC, 1986; EPA report 1992; Trédaniel et al., 1994). An outline of a number of the original contributions appears below. Critical comment is limited because the issue appears to be uncontentious at present.

The first report of a large study on passive smoking and lung function was that of White and Froeb (1980) which showed that non-smokers exposed to ETS for 20

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years in the workplace had small reductions in airflow compared with non-smokers not so exposed. This study had several flaws and no indication of how the ex-smokers were dealt with in the analysis. Lebowitz (1984) claimed that 3000 subjects were omitted from the report when the original data failed to show a difference.

Kauffman et al. (1983) found no difference in pulmonary function between non-smokers and passive smokers when the groups were considered as a whole, but when the analysis was restricted to subjects older than 40 years there was a statistically significant reduction in one measure of small airway function in passive smokers. For FEV_1 there was a statistically significant reduction of 90 mls for women, but no reduction in men. When the data for women passive smokers was further analysed by age it was found that there were significant differences in women only for the 30-35 age group and the 40-45 age group. The latter result argues against length of passive smoke exposure as an important determinant, a finding which is hard to reconcile with the hypothesis. In addition, male light smokers had better indices of small airway function than non-smokers while male passive smokers exposed to 20+ cigarettes per day had worse lung function than those who actively smoked 20+ cigarettes per day.

Brunekreef et al. (1985) in a small study from the Netherlands found small reductions in peak expiratory airflow in passive smoking women but FEV_1 was not statistically different. There was no increased rate of decline in FEV_1 with continued exposure to ETS.

In an analysis of the "MR FIT" data, Svendsen et al. (1987) reported that non-smoking males had, on average, an FEV_1 100 mls less if they were married to a smoker than if they were married to a non-smoker. However, the effect was less if the subject was married to a heavy smoker (42 mls) than if married to a light smoker (180 mls). When the data was averaged over all the visits there was only an insignificant difference of 2 mls between the groups. Workplace exposure was not considered in detail.

Masi et al. (1987) by using the technique of multiple linear regression in 293 non-smokers exposed to ETS in the home and in the workplace, found that men showed a reduction in some but not all measures of airflow if exposed to ETS in the home. There was no statistically significant reduction in airflow for workplace exposure but there was a mild reduction in vital capacity. For women the only measure that was statistically significant was a reduction in pulmonary diffusing capacity for workplace exposure to ETS.

In a Scottish study it was found that persons exposed to "high" levels of ETS had significantly lower adjusted FEV_1 compared with those with "low" exposure, but there was no difference between the low exposure group and controls (Hole et al., 1989).

Masjedi et al. (1990) in a study of 288 non-smoking Iranian adults found decrements in FEV_1, vital capacity and airflow in male passive smokers. In this group only workplace exposure was significant for the reduction of spirometric values. It is stated that 2 of the 288 subjects were excluded when "a history of smoking became apparent". As the study group consisted of delegates attending a medical conference, hospital workers and hospital visitors there may have been a denial of a smoking habit in a non-anonymous questionnaire.

In contrast with the above reports at least 9 studies have failed to detect a significant association between impairment of lung function and exposure to ETS (Schilling et al., 1977; Comstock et al., 1981; Jones et al., 1983; Lebowitz, 1984a & b; Kentner, 1984; Kryzanowski et al., 1986; Cotch et al., 1990; Laurent et al., 1992). These studies are not free of deficiencies in design and methodology but several have been conducted carefully.

Conclusion

Disregarding the possible deficiencies in many of the above studies, it is reasonable to conclude that population or specific-group based studies, whether cross-sectional or longitudinal, have failed to demonstrate a clinically significant long-term effect of ETS exposure on pulmonary function. These data do not exclude the possibility that small numbers of susceptible individuals may be at risk.

Association with chronic obstructive pulmonary disease

The detection of small numbers of individuals who develop pulmonary impairment as a result of chronic exposure to ETS might be possible in case/control studies or studies designed to detect an association between symptoms or diagnosis of obstructive lung disease and ETS exposure. Several such studies have appeared.

In a Czechoslovakian study conducted between 1972 and 1975 subjects exposed to ETS at home were reported to suffer symptoms of "chronic bronchitis" more frequently than those not exposed (Simecek, 1980). Hirayama (1981) reported an

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increased relative risk for death from asthma and emphysema among non-smoking Japanese women married to smokers but the relative risk (RR) failed to reach statistical significance. A similar result was reported by Sandler et al. (1989). Kalandidi et al. (1987) reported that the risk of hospitalisation for "chronic obstructive pulmonary disease" among non-smoking women in Greece was significantly related to the amount smoked by the husband.

The Seventh Day Adventist studies from the U.S. have also reported an increased risk of chronic obstructive pulmonary disease for persons living with a smoker (Euler et al., 1987). In a more recent report from the same study (Abbey et al., 1991) increased relative risks for asthma and "bronchitis" were found with increased levels of total suspended particulates (RR's of 1.7 and 1.3, respectively) and ozone (RR's of 1.4 and 1.2). Although ETS is a major contributor to these variables, it is not the only source (e.g. see Lebowitz, 1984). However, with further analysis controlling for air pollution and childhood exposure to ETS, a cumulative relative risk for symptoms of obstructive lung disease was found (Robbins et al., 1993).

A similar association was reported by Dayal and coworkers (1994) following reanalysis of data originally collected in 1985-1986 as a probability sample survey of mortality in 9 neighbourhoods in Philadelphia. The odds ratio for passive smoking (more than one pack a day) being associated with a diagnosis of asthma, chronic bronchitis or emphysema was 1.86 (1.21-2.86). A major deficiency of this study was the random selection of case controls whereas genetic or other "shared" factors may have contributed to the association of disease with active smoking cases.

The major problem with all of these studies is that they fail to account for several potentially major confounding factors including genetic or acquired variation in lung function and shared environmental factors other than ETS possibly related to lifestyle. In a longitudinal study over 10 years Cotch et al. (1990) used the technique of path analysis to assess the relative importance of various factors which might influence lung function in 978 individuals from 384 families living in Baltimore. Genetic factors accounted for 36-40% of the variation in the adjusted FEV_1, while personal (i.e. active) smoking explained only 3 and 10% of the variation in FEV_1 in adult offspring and parents, respectively. Shared environmental factors *influencing* personal smoking were reported to account for 3-5% of the variation. Individual factors (other than genetic) that are constant over time accounted for approximately 42% of the variation. The remaining 15% of the

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variation in offspring and 8% in parents represented "unexplained residual factors", but the authors claimed that "very little" of the correlations in FEV_1 among relatives could be attributed to "shared smoking behaviour" or passive smoking. This study highlights the magnitude of genetic and cohabitational influences on lung function, the combined effects being substantially greater than even the influence of active smoking. Much of the passive smoking literature is based on studies of co-habitants, but fails to control for this factor.

4.1.2 Asthmatic Subjects

Acute exposure to ETS and lung function

The first study to investigate the acute effects of ETS on pulmonary function of asthmatics was undertaken by Shephard and colleagues (1979), who studied a heterogeneous group of 14 asthmatics ranging in age from 19 to 65 years and methacholine sensitivity or PC_{20} (concentration for 20% fall of FEV_1) ranging from 0.8 to 24 mg/ml. The group was exposed to machine generated ETS in a "heavily contaminated" environmental chamber (CO concentration about 24 ppm, comparable to exposures reported in bars and taverns). No significant changes were noted for measurements of lung volumes, FEV_1 or forced expiratory flows at 25 and 50% VC. When the subgroup claiming "sensitivity" to ETS was analysed separately, the only significant response to ETS exposure compared with sham was a paradoxical small *increase* in FEV_1.

By contrast, a second study (Dahms et al., 1981) showed significant decreases of about 20% in FEV_1, FVC and mid-expiratory flows after 1 hour exposure to ETS (CO concentration estimated to be 15-20 ppm). As for the earlier study, no significant effects were seen in control subjects. The decline in lung function was progressive over the 60 minutes and reversed completely 15 minutes after bronchodilator. The 10 asthmatics in this study differed from those studied by Shephard et al., in that they were younger (18-26 years) and had marked bronchial hyper-responsiveness (PC_{20}%, FEV_1 for methacholine 0.075-1.25 mg/ml). There was an apparent relationship between methacholine and ETS sensitivity but it did not reach statistical significance. Half of the subjects in each group claimed to be "sensitive" to ETS.

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In an attempt to resolve the discrepancy raised by these two studies, seven more reports have appeared in the literature: three were negative and four show variable effects, at least for some asthmatic subjects.

Knight and Breslin (1985) studied 6 asthmatics exposed to an unspecified concentration of ETS and found significant declines in FEV_1 and mid-expiratory flow rates after 1 hour in 3 subjects and smaller declines in the other 3. There was also a trend for the PC_{20} for histamine to fall after exposure (pre-challenge range 0.22-7.2 mg/ml).

Stankus et al. (1988) recruited 21 "smoke-sensitive" asthmatics from respondents to newspaper advertisements (19 atopic, age range 21-50 years). Two of the subjects had a 20% fall in FEV_1 after 2 hours of the "low-level" exposure (CO about 9 ppm), while 5 others reacted to a second or third challenge at "high" (CO 13 ppm) or "ultra-high" (CO 14 ppm) levels. The remaining 14 had minimal reactions at any level. The results for individual subjects were reproducible on repeated testing. These authors stated that there was no association between smoke sensitivity and methacholine sensitivity, but data for the latter were presented in "breath units" which are not easy to correlate with other results. Furthermore, there was no observed association between a positive smoke challenge and the presence of serum IgE antibodies and/or a positive skin test to tobacco leaf extract.

In a subsequent study these authors performed methacholine challenges serially after smoke challenge (Menon et al., 1992). In this study only 5 out of 31 "sensitive" asthmatics and no "sensitive" controls had significant falls in FEV_1. Almost 30% of the asthmatics had heightened bronchial reactivity at 24 hours which persisted for 2 weeks in about 10%. The latter were presumably the three subjects who showed a 10-fold decrease in the PD 20%. The remainder had relatively small changes. The results for non-asthmatics were qualitatively similar with 18% increased at 6 hours and 8% at 3 weeks. There was no correlation between the change in methacholine sensitivity and the decline in FEV_1 in response to smoke challenge. These results are not generally applicable because *all* subjects were atopic and "sensitive" to ETS. Only 3 of the asthmatic subjects were using preventive medications. There was no attempt to control for confounding causes of changes in bronchial reactivity such as occupational exposures. An extra control group of 6 asthmatics performed serial methacholine challenges without any ETS exposure but their results were not reported.

In an attempt to control for psychological influences, which are known to be capable of provoking bronchospasm in susceptible asthmatics, Danuser and coworkers (1993) reported exposing subjects to increasing concentrations of ETS (CO 0-32 ppm) for 2 minutes through a valve box and mouthpiece, with the expired air diverted from the room. This largely removed any upper respiratory or ocular symptoms and subjects were generally unaware of the dose level. A clear cut dose response was observed for symptoms of cough and throat irritation in both the control subjects and those with documented bronchial hyperresponsiveness. There was no change in FEV_1 or mid-expiratory flows in the control subjects. For the reactive subjects, the greatest decline in function occurred at the lowest concentration (2 ppm CO), with relatively small and variable changes thereafter. The maximal decline in FEV_1 was less than 10% on average. This study lacked a "sham" experiment day. A 10% fall in FEV_1 could be expected in sensitive asthmatic subjects asked to perform 7 sets of spirometry interspersed with periods of breathing for 2 minutes on a mouthpiece.

In contrast with the positive studies reported above several carefully conducted studies have shown no significant acute effects of ETS exposure in asthmatic subjects. Wiedeman et al. (1986) reported exposing 9 young asthmatic subjects with moderate or marked bronchial hyperreactivity (age 19-30 years, PC_{20} for methacholine 0.25 mg/ml; all subjects less than 1.0 mg/ml) to one hour of high concentrations of ETS (40-50 ppm CO in an environmental chamber). There were no significant changes in FEV_1 or mid-expiratory flows and a paradoxical significant *decrease* in bronchial reactivity to methacholine following exposure (from 0.25 mg/ml to 0.79 mg/ml).

Similar results were reported by Magnussen and colleagues (1992) (see also Jörres & Magnussen, 1992) who studied 24 asthmatic (PC_{20}, 0.23 mg/ml) and 16 control subjects. Compared with sham conditions exposure for 1 hour to ETS (20 ppm CO) produced no significant change in FEV_1, airway resistance or bronchial reactivity. All subjects (asthmatic and control) complained of significant discomfort during exposure. The actual symptom scores for asthmatics did not correlate with their pre-exposure histories of sensitivity to ETS.

Summary and conclusions

The literature provides conflicting data concerning the acute effects of exposure to ETS on lung function and bronchial reactivity in asthmatic subjects. At least some of the discrepancies might be explained by differences in subject selection and

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exposure conditions. A number of conclusions can be drawn from the available data.

(i) Clinically significant bronchospasm as a result of exposure to very high levels of ETS appears to be a rare event. Decreases in FEV_1 of 20% or more have been observed in some asthmatics with moderately severe bronchial hyper-responsiveness and pre-existing intolerance to ETS.

(ii) All the reports of positive effects indicate prompt reversal of bronchospasm within 15 minutes of inhalation of a beta agonist to values equal to or higher than those observed pre-exposure. Pre-treatment with a beta agonist will prevent bronchospasm in "sensitive" asthmatics. Inhaled sodium chromoglycate may also prevent airway reactions.

(iii) The possible protective effect of adequate prophylaxis with inhaled steroids or sodium chromoglycate ("Intal") has not been investigated systematically.

(iv) There is marked individual variability in airway responses to ETS exposure ranging from significant declines to significant increases in FEV_1. There appears to be a weak association between reactivity to ETS and reactivity to methacholine or histamine when the analysis is restricted to subjects who react negatively to ETS, but conflicting results have appeared.

(v) A dose response relationship between ETS exposure and decline in airway function has not been documented conclusively and there is some contradictory data. For example Danuser et al. (1993) observed the greatest relative change after only 2 minutes breathing ETS at the lowest concentration (2 ppm CO), with some subjects showing improvements at higher levels, although there was a weak overall trend towards a gradual decline. By contrast, Stankus et al. (1988) claimed that duration of exposure was important with some of their seven reactors requiring two or three exposure periods (at increasing concentrations) before a significant decline was detected. The highest exposure levels reported were those of Weideman et al. (1986; 40-50 ppm CO) and these produced no consistent effects in young asthmatics with at least moderate bronchial hyper-reactivity, two thirds of whom complained of "sensitivity" to ETS and more than half had previous admissions to hospital for asthma.

(vi) The short and long term effects of ETS exposure on bronchial hyper-responsiveness have not been consistent. Two studies showed significant increases in bronchial hyper-responsiveness, two showed no effect and one showed a significant improvement. The latter finding is concordant with the results of Bolin et al. (1980) who documented a significant *increase* in bronchial reactivity in asthmatics who were successful in ceasing active smoking (PC_{20} for methacholine decreased from 5.62 to 1.56 mg/ml). In other words, in this group of asthmatics, cessation of active smoking appeared to have a deleterious effect on bronchial hyper-responsiveness.

(vii) The prevailing view is that the short term effects of ETS on asthmatic airways are those of irritation possibly mediated by nociceptive afferent neurones. There are no data to support the view that reactions, when present, involve IgE mediated hypersensitivity and there is no evidence of typical late reactions at 6-8 and 24 hours after exposure.

Chronic exposure to tobacco smoke and lung function

Few studies have examined specifically the possible long-term influences of chronic or recurrent ETS exposure on morbidity and lung function in asthmatic subjects. However, a number of epidemiological reports on active and passive smoking have analysed asthmatics separately and a number of conclusions can be drawn from this literature.

Almost all studies indicate that the diagnosis of asthma is associated with an excessive rate of decline of airway function which is at least double that for non-smoking, non-asthmatics and comparable to or exceeding that of active smokers. Numerous cross-sectional studies have shown that unselected asthmatics have impaired airway function compared with matched control subjects. This has been documented also in a group of asthmatics after intensive therapy for 4 weeks including oral corticosteroids (Brown et al., 1984). The reduction in FEV_1 (compared with predicted) correlated with duration and severity of asthma, but not with a history of active smoking. Females showed a significantly greater decline with age than men. Other cross-sectional studies have failed to document significant additional impairment in smoking asthmatics (e.g. Higenbottom et al., 1980).

In contrast with the above results the cross-sectional study of Connolly et al. (1989) reported that, in addition to age and duration of asthma, poor control of

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wheeze was related to lower social class, current smoking and lack of central heating. Persistent obstruction was related to age and duration of asthma, lifetime amount smoked, and lack of central heating. However, it is not clear whether smokers with chronic airflow limitation and partially reversible obstruction were included as asthmatics. There may also have been some reporting bias of smoking status because the influence of passive smoking appeared to be of greater magnitude than a history of past smoking. This is not consistent with other studies which showed marked impairment of function and increased bronchial hyper-responsiveness in asthmatics who are ex-smokers.

The longitudinal study of the population of Busselton, Western Australia (Peat et al., 1990) showed that asthmatics had lower baseline lung function and a greater annual decline of FEV_1 compared with non-smoking normal subjects (50 ml/year versus 35 ml/year). There was wide individual variation in the annual rate of decline with some subjects exceeding 90 ml/year. The rate of decline correlated with the degree of bronchial hyper-responsiveness but not with atopic or smoking status. Among the asthmatics, 39% were current smokers.

The above results are consistent with those from an 8-year longitudinal study in Montreal (Jaakkola et al., 1993). Subjects with "doctor-diagnosed asthma" had an *excess* annual decline in FEV_1 of 43 ml/year greater than that observed for asymptomatic normals. This exceeded the excess decline seen in symptomatic current smokers whether they had asthma or not. Indeed, the excess annual decline was less for current smoking asthmatics than those who had never smoked. That this might reflect a "healthy smoker effect" is supported by the observation that the greatest annual decline was seen in asthmatics who were ex-smokers. Alternatively, the ex-smokers might have developed an increase in bronchial reactivity after cessation (see Bolin et al., 1980).

In a recent study of the long-term benefits of inhaled corticosteroids in patients with chronic airflow limitation it was found that, among those who had documented bronchial hyper-responsiveness, the single independent predictor of a favourable response was the baseline bronchodilator response (Kerstjens et al., 1993). Smoking status was not a significant predictor.

Most of the epidemiological studies which have examined possible influences of passive smoking on pulmonary function in adults have specifically excluded asthmatics from analysis. As part of a prospective study of obstructive lung diseases in Tucson, Arizona, Lebowitz (1984) reported that airway function and "asthma attacks" in adult asthmatics related to room temperature, high humidity,

micropollen and indoor total suspended particulates, but not to passive smoking *per se*.

Connolly et al. (1989) undertook a study of "all asthmatics" attending a specialist clinic in Edinburgh. The potential influence of social and environmental factors was assessed from the patient history. About half the patients were on oral corticosteroids and a third on inhaled steroids or sodium chromoglycate. Passive smoking was associated with a reduction in airway function, but there were some anomalies in the results. Passive smoking was as strongly associated with function as current active smoking while total amount smoked and ex-smoker status were not significant predictors. The data provided were insufficient to allow critical appraisal.

In a longitudinal study of young adults over an 8 year period the diagnosis of asthma and/or the development of wheeze and dyspnoea were associated with an excess decline in lung function (Lebowitz, 1980). The presence of atopy was a significant modifier but gender and exposure to ETS were not.

Conclusions

Asthma in adults is associated with an overall impairment of airway function and an excess rate of decline with time, the magnitude of which is comparable to or exceeds that for active smokers. Active smoking appears to have little effect on this rate of decline, but a "healthy smoker" effect (in which those who are affected managed to cease smoking) cannot be excluded. Given the variability of airway function that characterises asthma and the excess mean annual decline, it would be very difficult to detect a small additional influence of passive smoking. However, Lebowitz (1984) was able to document significant interactions between airway function in asthmatics and several environmental factors, but not ETS.

The available data do not support the hypothesis that asthmatics represent a group particularly susceptible to long-term respiratory effects of ETS.

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4.2 LUNG CANCER IN ADULTS

4.2.1 EPIDEMIOLOGICAL STUDIES

There has been a number of well publicised reviews of the epidemiological, experimental and biological data contributing to the assessment of a potential causal link between ETS exposure and lung cancer in adults. These include reports by the Surgeon General (1986), NH&MRC (1986), NRC (1986), EPA (1992) and OSHA (1994).

Although these reports are considered by many to be authoritative and scientifically sound, some problems have been identified with methodology and reporting.

The conclusions of the EPA Report (1992) have been debated by Lee (1994), Gross (1994) and Huber et al. (1993), among others. The bases for their criticism include the following weaknesses:

- failure to consider all the epidemiological evidence including workplace and childhood exposure data
- difficulties with interpreting weak associations
- failure to adjust appropriately for confounding variables
- inadequate correction for misclassification bias and active smoking status
- failure to explain the lack of consistency between results for different countries
- failure to account for publication bias

The 1994 Occupational Safety and Health Association (OSHA) Report is concerned with occupational exposure but does not appear to formally evaluate the workplace evidence (see below for a summary of this). Instead it uses an arguably invalid extrapolation from an incorrect summary of spousal exposure studies. These points are argued forcefully in Tweedie (1994) and Layard (1994).

In view of the identified weaknesses in the public reviews we also conducted detailed assessments of all of the available individual studies on the association between exposure to ETS and lung cancer. In addition we have used other published reviews including those of Wells (1993), Lee (1992, 1994), LeVois and

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Layard (1994), Smith et al. (1992), Pershagen (1994), Mengersen et al. (1994) and Tweedie and Mengersen (1994).

Exposure to Spousal Smoking

Overall Association

Table 4.2.1.1 combines some details and results from Mengersen et al. (1994), Lee (1992) and Lee (1994) of all studies known to us, through Medline and Cancerlink searches and reference to the above published reviews, which provide comparable data relevant to the association between exposure to ETS and lung cancer in nonsmoking adults, using spousal smoking as the primary measure of exposure. This currently comprises 38 studies of which two are unpublished theses. Nine other related studies do not provide comparable data; Lee (1992, Section 3.1) and the EPA Report (1992) provide details of these and the reasons why they should be excluded from an overall assessment of the ETS-lung cancer relationship. In addition the studies by Katada (1988) and Sandler (1989) are not included because they lack the necessary information.

Table 4.2.1.1 shows that, for females with smoking husbands, out of 35 studies reporting unadjusted relative risks none were statistically significantly reduced, 29 were not significantly raised or lowered and 6 were statistically significantly raised (at the 5% two sided level). For males all of the unadjusted relative risks reported were not significantly raised or lowered.

Various meta-analyses have been conducted to examine whether a significant association between ETS and lung cancer can be derived: (Wald et al., 1986; NRC Report., 1986; Tweedie & Mengersen, 1992; EPA Report, 1992; Lee, 1993; LeVois & Layard, 1994). Smith et al. (1992) mentions 8 such meta-analyses and concludes that "all meta-analyses found summary risk ratios less than 2.0 (most less than 1.5) for non-smoking women married to smokers."

The EPA's (1992) meta-analysis of US studies omitted two studies published before the release of its report: Brownson et al. (1992) and Stockwell et al. (1992). LeVois and Layard (1994) report that "using the EPA's methods and assumptions, we have calculated a summary relative risk of 1.07 (95% confidence interval of .95 to 1.21) from a meta-analysis of 13 US spousal smoking studies including these two recent studies".

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Mengersen et al. (1994) use 34 studies, including more recent ones (see Table 4.2.1.1), and adopt the data tabulated in Lee (1992, Tables 3.13F and 3.13M) and comparable data from five more recent studies (including Fontham, 1994). Lee's (1994) meta-analyses include a study by Du et al. (1993) but not by Ger et al. (1993). He obtains meta-analysis based summary relative risks of 1.17 (95% confidence interval of 1.08-1.27) for unadjusted relative risks and of 1.14 (95% confidence interval of 1.06-1.23) using relative risks adjusted for covariates where available. These, and other summary relative risks, for various subgroups, reported by Lee (1994) are very similar to those obtained by Mengersen et al. (1994) and reported in the following.

Mengersen et al. (1994) present four basic analyses of the available results: (i) a fixed effects meta-analysis based on logit, (ii) test-based and (iii) Sato based calculation of RR and confidence intervals and (iv) a random effects model using logit based estimates. They also analyse the published data using unadjusted relative risks, adjusted relative risks and a combination of both. Overall the results are similar using the various methods and adjusted or unadjusted estimates of RR. However they argue that the use of the random effects (RE) model is more appropriate in this meta-analysis because of the heterogeneity detected by them between the studies. Their results are broadly supported under various models and assumptions, and based on somewhat different datasets (Lee, 1992; Besag et al., 1994).

The meta-analysis results of Mengersen et al. (1994) (for the RE model), are as follows. Quoted estimates are for RR and 95% logit-based confidence intervals.

- *For females exposed to smoking spouses.* Using unadjusted relative risks from 31 studies (3 of which are cohort designs, 28 of which are case-control) the overall relative risk is 1.20 [1.07, 1.35]. Using adjusted relative risks only, the overall relative risk is 1.28 [1.03, 1.59] and using adjusted relative risks where available and unadjusted otherwise the overall relative risk is 1.24 [1.08, 1.43]. Note that these adjustments are for different sets of confounders in each individual study.
- *For males exposed to smoking spouses.* Similar combined results are 1.39 [.95, 2.04], 2.01 [1.22, 3.30], 1.43 [.99, 2.06] respectively. Although the second value (that for adjusted relative risks alone) is elevated when compared to the other two summary results it is based on few studies with high reported adjusted *and* unadjusted relative risks. Thus it would be incorrect to conclude from this that adjustment for confounding factors results in larger relative risks in general.
- For US studies the overall relative risks using the RE model are 1.11 [.98, 1.26] for females and .95 [.58, 1.54] for males.
- For Asian studies the corresponding results are 1.27 [1.04, 1.56] for females and 2.28 [1.15, 4.52] for males.
- For "better quality" studies (Tiers 1 to 3 as judged by the EPA Report, 1992) the overall relative risks for females is 1.24 [1.12, 1.36] and for males is 1.39 [.95, 2.04]
- The degree of unexplained variation between the individual estimates indicates that possible confounders should be more closely investigated and that if an overall relative risk is to be ascribed to a population, a representative subgroup of studies should be used.
- This is reflected in the different estimates obtained for the different study groups delineated in the EPA Report: the overall *excess* risk for Asian studies is about twice that for US studies. Overall relative risks for the latter, for either sex, are not statistically significant at the 5% level.
- There is a strong indication of publication bias favouring raised relative risks, which may spuriously inflate these overall results.

Based on published data of overall relative risks for lung cancer associated with exposure to spousal smoking (in a variety of imprecisely defined forms) it can be concluded from this meta-analysis that the best estimates, although not attributable to chance, do not rise to the levels required for strength of association to be established (see Section 2.1 for details).

Exposure-Response

Table 4.2.1.1 identifies 17 case control and 2 cohort studies from Lee (1992, Tables 3.17 and 3.18) and EPA (1992, Table 5-11), which report on exposure-response relationships amongst females. One of these (Wu-Williams et al., 1990) reports only that there was no significant trend in risk. The most common exposure measures are cigarettes per day and years of exposure to spousal smoking. As measured by cigarettes per day, 7 of 16 studies reported significant trends at the 5% level. As measured by years of exposure, 3 out of 8 are reported to be significant at the 5% level.

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The EPA Report (1992) and Wu-Williams and Samet (1990) conducted an overall evaluation of this putative relationship "by eye". This was argued to be inappropriate by Tweedie and Mengersen (1992), who provided a number of formal meta-analytic approaches to exposure-response for the 16 case control studies. They also proposed that assessment of this relationship should be independent of the assessment of a possible overall association, and hence that the *unexposed* group should be excluded from the analysis. The rationale for this exclusion is that RR's greater than unity for exposures greater than zero may not differ from each other and yet the test for trend will be significant. In this case a trend may not be present in the RR for exposures above zero. Their main conclusions were as follows:

- When the unexposed group is excluded, there is no overall statistically significant relationship between lung cancer relative risk and level of exposure. This conclusion was also reached by Layard (1990).
- When the unexposed group is included, conflicting results have been reported, depending on the exposure measurement used and whether the model is forced through the point representing the unexposed group.

No study that we have examined has tested for alternative models such as a step function or other type of threshold response mentioned in Section 2.2, even though the data might indicate that these are more appropriate. Since two of the requirements for proof of causality are that an exposure-response be established and that results be consistent between studies it is clear from the epidemiological studies to date that:

(i) There is inconsistency between the results on exposure-response between the various studies.

(ii) A *non-threshold* exposure-response has not been established in any study because formal consideration and testing of the threshold possibility has not been carried out.

For example, Fontham et al. (1994) reports a number of dose-response assessments. Almost every type of exposure-response function listed in Section 2.2 could be inferred from or applied to these data. It is impossible to conclude from this particular study that there is a consistent biological gradient across the different reported exposures, especially since in a number of instances there is no significant elevation in risk until quite high exposures as measured by spousal smoking (above 40 pack years; see, for example, Table 3 of Fontham).

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Moreover the exposure response patterns presented for exposure by source (household, occupational and social) are implausible given the way in which each exposure was estimated.

In a number of studies the modelled response to ETS exposure appears to be higher than expected from corresponding results for direct exposure through active smoking. This provides additional inconsistency, not only between the studies concerned with the effects of exposure to ETS, but also with well established results for active smoking.

One possible explanation for an observed increased relative risk, but little indication of a positive exposure-response relationship, is that some bias may be inflating all of the observed risks (Layard, 1990; Tweedie & Mengersen, 1992). Such a rationale is in keeping with the results based on studies which used cotinine levels as an objective measure of exposure (see Tweedie & Mengersen, 1992).

As cautioned in Section 2.2, reporting bias could influence the assessment of exposure-response (Lee, 1994) and proper account must be taken for studies which do not report nonsignificant relationships.

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Table 4.2.1.1: *Studies which provide relative risk estimates of lung cancer for nonsmokers exposed to ETS, as measured by spousal smoking*

1st Author (Year)	*Country*	*Sex*	*Crude RR (95%CI)*	*Adjusted RR (95%CI)*	*Exposure-Response Trends[1] (Females only)*	
Case Control Studies						
Akiba (1986)	Japan	F	1.5 (0.9-2.8)	1.5 (0.9-2.8)	NS/*	(cig/day) [Lee/EPA]
		M	2.1 (0.3-9.6)	1.8 (0.4-7.0)	NS	(years)
Brownson (1987)	USA	F	1.8 (0.3-8.9)	1.7 (0.4-2.9)	NS	(cig/day)
Brownson (1992)	USA	F	1.0 (0.8-1.2)	1.0 (0.8-1.2)	NS	(pack-years)
Buffler (1984)	USA	F	0.8 (0.3-2.2)	-	NS	(cig/day)
		M	0.5 (0.1-2.2)	-		
Chan (1982)	Hong Kong	F	0.8 (0.4-1.4)	-		
Correa (1983)	USA	F	2.1 (0.8-6.1)	-	**	(pack-years)
		M	2.0 (0.2-11.8)	-		
Du (1993)	China	F	1.1 (0.6-1.9)			
Fontham (1994)	USA	F	1.3 (1.1-1.4)	1.3 (1.0-1.6)	*	(pack-years)
Gao (1987)	China	F	1.2 (0.8-1.8)	About 1.4	*/NS	(total years) [Lee/EPA]
Garfinkel (1985)	USA	F	1.2 (0.8-1.9)	-	*	(cig/day)
Geng (1988)	China	F	2.2 (1.0-4.6)	-	*	(cig/day)
					***/*	(years) [Lee/EPA]
Ger (1993)	Taiwan	F	-	1.2 (0.5-2.9)	***	(cigs/day)
		M	-	0.9 (0.1-6.5)		
Humble (1987)	USA	F	2.3 (0.8-8.6)	2.2 (0.8-6.6)	NS	(cigs/day)
		M	4.2 (0.8-28.0)	-		
Inoue (1988)	Japan	F	2.6 (0.7-11.9)	2.3 (0.8-8.8)	*	(cigs/day)
Janerich (1990)	USA	F	0.8 (0.5-1.2)	-		
		M	0.8 (0.3-1.8)	-		
		F&M	-	0.9 (0.6-1.5)	N/A	

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Table 4.2.1.1: *Studies which provide relative risk estimates of lung cancer for nonsmokers exposed to ETS, as measured by spousal smoking (cont.)*

1st Author (Year)	*Country*	*Sex*	*Crude RR (95%CI)*	*Adjusted RR (95%CI)*	*Exposure-Response Trends[1] (Females only)*	
Kabat (1990)	USA	F	0.9 (0.4-1.9)	-		
		M	1.2 (0.5-2.9)	-		
Kabat (1984)	USA	F	0.8 (0.2-2.8)	-		
		M	1.0 (0.2-6.7)	-		
Kalandidi (1990)	Greece	F	1.6 (0.8-2.9)	2.1 (1.1-4.1)	+	(cigs/day)
					NS/*	(years) [Lee/EPA]
Koo (1987)	Hong Kong	F	1.6 (0.9-2.8)	1.6 (0.9-3.1)	NS	(cigs/day)
					NS	(yrs at home or work)
Lam T (1987)	Hong Kong	F	1.7 (1.1-2.4)	-	**	(cigs/day)
Lam W (1985)	Hong Kong	F	2.0 (1.0-3.9)	-		
Lee (1986)	England	F	1.0 (0.4-2.9)	1.0 (0.4-2.7)		
		M	1.3 (0.3-5.4)	1.3 (0.4-4.4)		
Liu (1991)	China	F	0.7 (0.3-1.9)	-		
Pershagen (1987)	Sweden	F	1.0 (0.6-1.8)	1.2 (0.7-2.1)	NS	(cigs/day)
Shimizu (1988)	Japan	F	1.1 (0.6-1.9)	-		
Sobue (1990)	Japan	F	1.1 (0.7-1.6)	1.1 (0.8-1.6)		
Stockwell (1991)	USA	F	1.6 (0.8-3.2)	1.6 (0.8-3.0)		
Svensson (1989)	Sweden	F	1.3 (0.5-3.2)	About 1.5		
Trichopoulos (1981)	Greece	F	2.1 (1.2-3.8)	-	**	(cigs/day)
Varela (1987)	USA	F	0.8 (0.5-1.2)	-	NS	(years)
		M	0.8 (0.3-1.9)			

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Table 4.2.1.1: *Studies which provide relative risk estimates of lung cancer for nonsmokers exposed to ETS, as measured by spousal smoking (cont.)*

1st Author (Year)	Country	Sex	Crude RR (95%CI)	Adjusted RR (95%CI)	Exposure-Response Trends[1] (Females only)
Wang (1994)	China	F	0.8 (0.4-1.8)	0.9 (0.3-2.5)	
Wu (1985)	USA	F	1.2 (0.4-3.4)	1.2 (0.5-3.3)	NS/NA (years) [Lee/EPA]
Wu-Williams (1990)	China	F	0.8 (0.6-1.0)	0.7 (0.6-0.9)	'no significant trend'
Ziegler (1984)	USA	M	Less than 1	Less than 1	
Cohort Studies					
Butler (1988)	USA	F	2.4 (0.6-10.2)	2.0 (0.4-8.8)	
		M	2.5	2.0 (0.5-8.6)	
Garfinkel (1981)	USA	F	1.2 (0.8-1.6)	1.18	NA (but NS on our reanalysis)
Hirayama (1981)	Japan	F	1.4 (1.0-2.0)	1.5 (1.0-2.1)	*/** (cigs/day) [Lee/EPA]
		M	2.4 (0.9-5.2)	2.3 (1.2-4.2)	
Hole (1989)	Scotland	F	1.9 (0.2-9.0)	-	
		M	3.5 (0.2-208)	-	
		M&F	-	2.4 (0.5-12.8)	

Source: Mengersen et al. (1994), Lee (1992), Lee (1994).

Ex-smokers are excluded where possible. Individual studies account for different subsets of possible confounders
in the adjusted estimates. The estimate for Wang is adjusted for active smoking (Table 4).

[1] Taken from EPA (1992, Table 5-11) and Lee (1992, Tables 3-17, 3-18), Lee (1994).
Includes unexposed group.

NS $p>0.10$; + $0.10<p<0.05$; * $0.05<p<0.01$; ** $0.01<p<0.001$; *** $p<0.001$

Exposure to ETS in the Workplace

Table 4.2.1.2 provides details of 12 epidemiological studies which provide data on the association between lung cancer and general workplace exposure to ETS as extracted from Lee (1992, 1993), LeVois and Layard (1994) and Biggerstaff, Mengersen and Tweedie (1994).

The results of Butler (1988) are too unreliable to be useful in this assessment. In addition Brownson et al. (1992) and Stockwell et al. (1992) examined workplace exposure and observed, without reporting estimates or details of statistical tests, that there was no elevated relative risk with workplace exposure. It should be noted that the significant Fontham (1994) result is *not* adjusted for exposures in the home or at work.

Although the OSHA Report (1992) was commissioned to address the risk for workplace exposure, it ignores (without justification in the text) these data and bases its conclusions and recommendations on results from the studies on spousal exposure.

Biggerstaff et al. (1994) identified 11 studies which have a shared goal of measurement of the relative risk of lung cancer associated solely with "general" exposure to ETS in the workplace.

Five of the 11 studies with female respondents reported an increase in the relative risk of lung cancer associated with workplace ETS exposure, with just one of these significantly raised at the 5% level. For males, two of the three studies reported a raised point estimate of this relative risk, but neither of these was reported to be significant at the 5% level. Another study not included in the meta-analysis reported a risk of 0.0 for males because there were no cases (Butler, 1988).

Both Lee (1992) and Biggerstaff et al. (1994) conducted meta-analyses. Lee (1992, p. 117) reports an overall estimated relative risk of 0.98 and a 95% confidence interval of (0.89, 1.08) for published results in the nine studies available in 1986, and in (1993, Tables 4 and 5) gave revised (still non-significant) assessments and discussion. Biggerstaff et al. (1994) provide an independent assessment of the dataset in Lee (1993), using the two models considered by Lee and a further Bayesian approach. Their main conclusions are that for unadjusted data, there is an overall relative risk for females from 1.04 to 1.12 (depending on the method) and for males from 1.51 to 1.69, none of which is statistically significantly raised above unity at the 5% level. LeVois and Layard (1994) also conclude from the

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meta-analysis of worldwide (and for US studies separated out) that the summary relative risk is between .98 and 1.01 and is not significantly raised or lowered.

It can be concluded that from these data and analyses that:

(i) there is no overall statistically significant association between exposure to ETS in the workplace and lung cancer;

(ii) any effect of ETS exposure in the workplace as a cause of lung cancer is not supported by the epidemiological evidence.

Table 4.2.1.2: *Studies which provide relative risk estimates and confidence intervals of lung cancer for nonsmokers exposed to ETS, as measured by smoking in the workplace*

1st Author (Year)	*Sex*	*Crude RR (95% Exact CI)*	*Adjusted RR (95%CI)*
Fontham (1994)	F	1.1 (0.9-1.4)	1.4 (1.1-1.7)
Garfinkel (1985)	F	0.9 (0.5-1.6)	0.9 (0.7-1.2)
Janerich (1990)	F/M	-	0.9 (0.8-1.0)
Kabat (1990)	F	1.0 (0.5-2.2)	-
	M	1.0 (0.5-2.1)	1.0 (0.5-2.1)
Kabat (1984)	F	0.7 (0.3-1.6)	-
	M	3.3 (1.0-10.6)	-
Kalandidi (1990)	F	1.4 (0.7-2.7)	1.1 (0.2-4.9)
Koo (1987)	F	0.9 (0.1-7.0)	-
Lee (1986)	F	0.6 (0.1-2.5)	-
	M	1.6 (0.4-6.6)	-
Shimizu (1988)	F	1.2 (0.7-2.1)	-
Svensson (1989)*	F	1.1 (0.7-2.0)	1.2 (0.4-2.9)
Wu (1985)	F	-	1.3 (0.5-3.3)
Wu-Williams (1990)	F	1.2 (0.9-1.6)	-

Source: Biggerstuff et al. (1994), Lee (1992, 1994), LeVois and Layard (1994)

* combines workplace and home exposure.

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Exposure to ETS in Childhood

According to Lee (1994, Table 4.2.1.2) there are 16 studies with results on lung cancer in adulthood associated with childhood ETS exposure; he reports a meta-analysis which gave unadjusted and adjusted relative risk estimates less than unity, implying no positive association.

Determination of childhood exposure is likely to be much more inaccurate than assessing adulthood exposure and hence more caution is needed in interpreting any results. In the Fontham et al. (1994) study, results are reported for the association between risk of lung cancer and childhood exposure to tobacco smoke among nonsmoking women. Regardless of source of exposure (father, mother, other household member) and regardless of histological type (adenocarcinoma versus other), no crude or adjusted odds ratio was significantly different from unity at the 5% level, with the majority of point estimates less than unity. Furthermore, in Fontham (1994, Table 5) the responses among non-smoking women to smoke-years of household exposure during childhood show negative (but nonsignificant) trends.

In spite of this, Fontham concludes (p.1759) that the increased risk of lung cancer from exposure to ETS is more marked for women also exposed in childhood. Reanalysis of the table indicates that a more plausible explanation of their results is that they observed surprisingly few cases who were exposed in childhood but not in adulthood.

Pershagen (1994) provides a summary of fifteen results contained in 10 studies which contain information on ETS exposure in childhood from various family members. He states that "only the study by Janerich et al. (1990) provided clear evidence of an increased lung cancer risk related to ETS exposure in childhood or adolescence. No consistent association was evident from the other studies, although two of three studies suggested an increased lung cancer risk if the mother smoked." Interestingly what Pershagen does not comment on (but is evident in his Table 4) is that the only statistically significant result is from the Janerich study for childhood exposure to greater than 25 smoker years (RR of 2.07 with a 95% confidence interval of 1.16 to 3.68). This is an extraordinary exposure level in which other biases and confounders could well be at work.

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In conclusion the overall epidemiological evidence indicates that exposure to ETS in childhood is not significantly associated with an increase in relative risk of lung cancer. Hence the epidemiology cannot support a conclusion of causality of lung cancer from childhood exposure.

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Table 4.2.1.3: Studies which provide relative risk estimates of lung cancer for adult nonsmokers exposed to ETS in childhood

1st Author (Year)	*Sex*	*Exposure Measure*	*Reported RR (95%CI)*
Akiba (1986)	M&F	Maternal or paternal smoking	No association
Correa (1983)	M&F	Maternal or paternal smoking	No significant increase in risk
Fontham (1994)	F	Exposed in childhood:	
		-to father's smoking	0.8 (0.7-1.0)
		-to mother's smoking	0.9 (0.6-1.2)
		- to any household member's smoking	0.9 (0.7-1.1)
Gao (1987)	F	Lived with smoker in childhood	1.1 (0.7-1.7)
Garfinkel (1984)	F	Exposed in childhood	0.9 (0.7-1.1)
Kabat (1984)	F	Exposed from family members	1.7 (0.9-3.3)
	M	Exposed from family members	0.7 (0.3-1.6)
Koo (1987)	F	Household exposure to cig.smoke	0.6 (0.2-1.8)
Pershagen (1987)	F	Parents smoked	1.0 (0.4-2.3)
Sobue (1990)	F	Smoking by father	0.8 (0.5-1.2)
	F	Smoking by mother	1.4 (0.8-2.5)
Svensson (1989)	F	Father smoking at age 0-9yrs	0.9 (0.4-2.3)
	F	Mother smoking at age 0-9yrs	3.3 (0.5-19)
Varela (1987)	M&F	Smoking by household members before age 21	1.3 (0.9-2.0)
Wang (1994)	F	Household exposure aged 0-6yrs	3.5 (1.8-6.7)
	F	Household exposure aged 7-14yrs	3.1 (1.6-5.9)
	F	Household exposure aged 15-22yr	3.1 (1.5-6.3)
Wu (1985)	F	Parents in childhood	0.6 (0.2-1.7)
Wu-Williams (1990)	F	Father smoked	1.1 (0.8-1.4)
	F	Mother smoked	0.9 (0.7-1.1)

Data are taken from Lee (1992, Table 3.23) where available. For Fontham (1994) adjusted relative risks are predicted. Fontham's figures should be regarded with caution; see discussion.

Wang's study group includes active smokers.

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4.2.2 Studies Using Markers for ETS

The EPA Report (1992) and Samet (1994) provide a literature on biochemical studies which attempt to evaluate the putative association between exposure to ETS and lung cancer.

Overall, the relative risk estimates for lung cancer associated with exposure to ETS, based on the cotinine data and extrapolation from active smoking data, are consistently smaller than those observed in the epidemiological studies. One reconciliation of the discrepancy, proposed by Tweedie and Mengersen (1992), is that the latter are biased upward by misclassification of active smokers; after adjusting for this they obtain consistent estimates from the two sources.

Attention has also been paid to differences between sidestream smoke (SS), mainstream smoke (MS) and ETS. Rodgman (1992) claims that there are fundamental physical and quantitative chemical differences among the three. Furthermore, partly because of the differences in inhalation amounts and retention percentage, the 'dosage of ETS retained is minuscule relative to MS'. He argues that there is a threshold effect for exposure to ETS, based on data about tumorigenicity of the ETS components. Given that the active smokers must be exposed to much higher concentrations and lifetime cumulative doses of all forms of tobacco smoke, it is implausible that these differences in biochemical properties of SS and MS could account for the inconsistencies in the literature.

4.2.3 Study Quality

The quality of the individual studies that comprise the body of literature on passive smoking and lung cancer has come under substantial scrutiny; (see, for example, Lee, 1992, 1993; EPA Report, 1992).

The influence of bias, misclassification and confounding has not always been adequately ruled out as a possible explanation for the observed excess risk when observed. Caution should be taken in interpreting the reported results of individual studies or of any meta-analyses which do account for these problems.

Major quality issues which, in our opinion, are potentially sources of substantial bias, are discussed below.

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Definition of Exposure

Problems with definition of exposure (discussed in Section 2.2.2) apply here. These include poor measurement, multiple sources, temporality, degree and duration.

Definition of Outcome: Histological Type

Mengersen et al. (1994) provide some discussion on the association between exposure to ETS and different histological types of lung cancer. Table 4.10 in the EPA Report (1992) lists twelve studies which have investigated this association. The studies differ in nomenclature, criteria and verification of tumour classification, and, the small size of many of the patient groups, resulted in unstable risk estimates, particularly in women. Lee (1992) also provides tables of the distribution of lung cancer cases by type of cancer (Table 3.4, p.88) and of relative risks by type of cancer (Table 3.16, p.110). More recent studies include Ger et al. (1993) and Fontham (1994).

Based on all these data, we find no consistency in the evidence about exposure to ETS and histological type of lung cancer associated with spousal exposure. Mengersen et al. (1994) provide details of results from fourteen studies which report on the association between different cell types and exposure to workplace smoking for nonsmoking subjects. Again, no consistent results with respect to cell type arise from these studies.

Results on histological type of cancers appear to be inconsistent, both between studies and with respect to the distribution expected if ETS is considered to have similar effects to active smoking (as assumed by the EPA in its report). For example Lee (1994) states that "one would [under this assumption] expect to find any association with ETS to be more clearly seen for squamous-cell cancer. In fact the evidence is conflicting regarding the histological type where the association is strongest."

Various biological models have been proposed to link ETS exposure with different histological types of lung cancer. There does not appear to be a clear, agreed view about which cell types would be more susceptible to exposure to ETS. Unfortunately the epidemiological literature provides no assistance in resolving these various theories with some studies indicating elevated relative risk for adenocarcinoma, others for small cell and squamous cell carcinoma.

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These observations illustrate a critical point about the studies to date. Either the observed significant associations between ETS exposure and a given cell type are due to chance (in which case the key test for causality that a sufficiently strong relationship is established fails) or, if not due to chance, then there is inconsistency between various papers (in which case another key test for causality fails). Thus, consideration of the results concerning cell type shows that they cannot support causality on three grounds: lack of strength of association, lack of consistency and no clearly established and accepted biological plausibility.

It is unrealistic with the size of studies completed to date to expect that they could support one particular biological hypothesis over another. For the present, and until more extensive studies are completed, it seems reasonable to define the outcome of interest to be "lung cancer of any histological type" and consider the studies individually or in composite using this outcome measure alone.

Misclassification

Misclassification of active smokers, or previous smokers, as never smokers will spuriously increase estimates of relative risk of lung cancer associated with exposure to ETS. Pron et al. (1988) and Brownson et al. (1992) discuss reliability of passive smoking histories reported in their case control studies. Tweedie et al. (1994) provide a recent model of misclassification of active smokers as nonsmokers in a case-control study, using data obtained from epidemiological and related studies. They show that, with quite reasonable assumptions, relative risk estimates could be inflated to 1.46 when no excess risk is in fact present. Lee (1992) also provides details of this phenomenon. LeVois and Layard (1994), using a reportedly more realistic misclassification rate of 2.5%, recalculate a summary relative risk of 1.00 (95% confidence interval of 0.89 to 1.14) from 13 US studies and suggest that application of US derived misclassification rates to other countries could be quite erroneous.

Data appear to be emerging that support the view that misclassification rates differ between countries and these differences might explain some of the differences in observed relative risks between various countries. If misclassification does differ between various countries (and possibly different demographic groups within single countries) then any meta analysis of the various studies should attempt to adjust for this. Misclassification of outcome is

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also a potential problem. In many studies lung cancer is not histologically established or is recorded from surrogate reports.

Lee (1992, pp.128-130) states that misclassification of diagnosis and of ETS exposure are not insubstantial but are unable to explain, on their own, the totality of observed association.

Surrogate Responses

Mengersen et al. (1994) have assessed the impact of the use of surrogate responses on the observed association between lung cancer and exposure to spousal smoking, for which 16 studies provide relevant data.

Their conclusion is that although the use of surrogate data affects study results, it does not do so in a systematic way.

Confounders

It is our opinion that control of confounders has not been adequate. LeVois and Layard (1994) summarise many of the key problems and provide numerous references. They state: "In fact, nearly every potential confounder that has been identified is likely to inflate a risk estimate derived from spousal smoking data. None of the ETS-lung cancer epidemiological studies adequately accounts for the effects of most of the known potential confounders."

For example, Smith and Liu (1994, Table 10) report significant odds ratios of 9.2 and 15.0 respectively for women who have cooked for 31-44 years and >45 years respectively. In the same study passive smoking exposure in the women yielded an odds ratio of .9 (not significantly different from 1.0). As a second example, rather strong conclusions about the role of diet in lung cancer formation or prevention are given in Tables 1 and 2 of Byers (1994), where a summary of numerous studies from a variety of countries on the association between low dietary intake of Vitamin A or Carotene shows that 34 results had an increased risk and 2 showed a decreased risk. The increased relative risks ranged from 1.0 to 7.2 with two thirds of the relative risk values being above 1.5.

Many of the relative risks are of similar or greater magnitude than those ascribed to ETS. This is supported by Katzenstein (1992) and Lee (1992); see Section 2.2.1. Lee (1992, Table 3.1.2) provides details of the different adjustments for confounders which were referred to in the individual studies.

It is impossible, within even the largest studies in the collection, to detect as significant at the 5% level a risk factor with a relative risk of under about 1.3. However three factors, each having a relative risk of 1.1, if present together would induce (assuming no interaction positively or negatively between them) an observed relative risk of 1.33. It is impossible that confounding risk factors of this magnitude would be detected in the studies we have examined. Hence although these risk factors would not be detected, they could, in aggregate, produce a relative risk at least as large as that observed for exposure to ETS.

The argument just presented could explain why some studies find it necessary to adjust for certain putative risk factors while others do not find evidence to adjust for the same factors.

There remains the possibility that a confounder or combination of confounders may provide an explanation for the observed excess risk and, further, severely restrict the applicability of the results to other populations.

Publication Bias

Mengersen, Tweedie and Biggerstaff (1994) demonstrated graphically that such bias exists for the association with lung cancer based on exposure to spousal smoking. Similar conclusions were reached by Lee (1994) who presents summary analyses based on a random effects meta-analysis for groups of studies of various sizes. His results are:

Study Size	Number of Studies	Unadjusted Relative Risks	Adjusted Relative Risks
At least 100 Cases	10	1.11 (0.96, 1.29)	1.12 (0.93, 1.33)
50 to 100 Cases	14	1.28 (1.06, 1.55)	1.35 (1.11, 1.64)
Under 50 Cases	13	1.48 (1.11, 1.97)	1.42 (1.07, 1.90)

These results are consistent with a publication bias against smaller non-positive studies.

Such publication bias may make invalid the EPA (1992) approach to combining study results which counts the number of positive (but not necessarily statistically significantly positive) studies and assesses the chance of observing the number of

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such positive studies. Of course if negative studies are not published they will be excluded from the counting.

Statistical Analysis

In most of the studies considered there is insufficient explanation provided about the exact statistical methods used to analyse the data. Often other critical information is omitted so that effects on bias in the results cannot be determined. As an example, in Fontham et al. (1994), there is considerable fluctuation in sample numbers used in various tables throughout the report. No explanation is provided for this. We could assume that they are a result of "item non-response" and this would certainly be consistent with use of surrogates for case questionnaire completion. However we do not know this.

Moreover, there are many unexplained aspects of methodology that prevent adequate comment being made on the validity of the results presented in Fontham et al. (1994) and other reports. Without further independent re-analysis or alternative analysis based on sensible assumptions and models the reliability of the weak relative risk estimates reported in the various studies reviewed here is questionable.

Representativeness

A number of reviews have identified concerns about the representativeness of subjects in individual studies and the applicability of overall results to particular populations (EPA Report, 1992; Lee, 1992; Mengersen et al., 1994).

The first issue is important when evaluating the individual relative risk estimates, since there is potential for substantial bias if the subjects are not drawn randomly from the target population, if there is a large nonresponse or dropout rate, or if cases and controls are not comparable with respect to important risk factors.

In some of the studies on ETS and lung cancer, the control groups include somewhat extreme subgroups (A-bomb survivors, Akiba; those with high cancer risk; Hole), patients with other types of cancer, other hospital patients, subjects of other health studies and people drawn from the general population. It may be argued that a relative risk that is observed over such different groups lends support to a causal relationship. However, these differences should be more thoroughly considered before allowing such support. Lee (1992, Table 3.5 and text) provides quite detailed discussion of this issue. Lee (1994) compares the use

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of studies which employ healthy controls with studies which use diseased controls and finds an indication that the use of diseased controls leads to an elevation in relative risk attributed to exposure to ETS.

Overall estimates obtained from a meta-analysis may not be applicable to particular populations. The above reviews have all identified substantial differences in risk estimates between countries. One possible explanation of this is that important region specific confounders have been ignored. LeVois and Layard (1994) report a highly significant (P-value < .001) inconsistency between the summary relative risks for six country-specific groups of female spousal studies considered by the EPA (1992). It is more likely that these differences are the product of uncontrolled biases and confounders which vary from region to region.

Study Size

Overall the studies provide information on about 4000 cases, the great majority of whom are females and over half of whom are from Asian countries.

Although many studies contain a substantial number of enrolled subjects, the analyses of nonsmokers or neversmokers by outcome and level of exposure are often based on quite small numbers which is reflected in wide confidence intervals. This exacerbates any effect of poor study quality, reduces the ability of the study to detect a real increased risk and obscures potential exposure-response relationships. Wu (1985) and Lee (1986) have only 10 unexposed cases, while the analyses of Hole (1988), Humble et al. (1987) and Inoue (1988) are based on even smaller numbers of cases (n=1, 5, 4 respectively). Any observed statistical significance (or lack of it) should be evaluated in light of these sample sizes.

4.2.4 Does Exposure to ETS Cause Lung Cancer in Adults?

We now address each of Hill's criteria for causation.

Strength

It is our opinion that the observed association is not strong. This is based on the following observations:

Chance: Of the studies of females identified in Tables 4.2.1.1, 4.2.1.2, 4.2.1.3, chance is not ruled out as a possible explanation in most of them.

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Overall, a statistically significant increase in relative risk of the order of 10-20% has been derived through meta-analysis. A smaller and nonsignificant overall excess risk has been found for females exposed to smoking in the workplace. Although the point estimates for the two sources of exposure are greater for males, they are not significantly different from unity and their interpretation is difficult due to the great variation in individual estimates.

Study Quality: Problems in the quality of individual studies have been identified by most authors and groups who have reviewed the literature and are summarised above. These have not been addressed with sufficient rigour in the literature to determine whether these problems could account for the observed excess risk. As discussed in detail above, increases in relative risk of the order of 10-20% could be explained readily by misclassification of a small number of cases.

Confounders: There are a number of risk factors for lung cancer. Similarly, there are many sources of the constituents of ETS. The individual studies are inconsistent in their selection of and adjustment for confounders. Moreover, the variability between estimates may indicate that important confounders have been overlooked, casting doubt on the representativeness of any overall observed association.

We conclude that confounders have not been adequately ruled out as possible explanations of the reported association.

Consistency

In contrast to the conclusions of the EPA (1992) we are of the opinion that the requirement of consistency is not satisfied by the body of literature.

Of the studies based on spousal exposure which are listed in Table 4.2.1.1, eight report an unadjusted relative risk which is less than (but not statistically significantly different from) unity; five are significantly greater than unity. Two remain less than unity after adjustment for some (different) confounders, and only three of the positive studies reporting confidence intervals are statistically significantly positive. For the studies based on workplace exposure eight of the eighteen reported relative risks are less than unity; only two are statistically significant.

Consistency also fails to be established between countries (with no agreed explanation for the observed inter-country differences).

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As discussed above there is also considerable lack of consistency between results for different histological types and for differing sources and amounts of ETS exposure.

Specificity

That lung cancer may have many possible causes is clear from the recent review volume of Samet (1994). There it is suggested that (page v.) "lung cancer has causes other than cigarette smoking: Exposure to arsenic, asbestos, chloromethyl ethers, radon progeny, and other agents in the workplace; outdoor air that has been contaminated by carcinogens generated by power plants, industry and vehicles; indoor environments, such as homes, schools and businesses where radon is omnipresent, have all been linked to increased lung cancer risks. Even non-smokers inhaling the smoke generated by active smoking are at some risk of lung cancer". Some of the literature that supports this statement appears to be speculative and (apart from literature on exposure to ETS and lung cancer) has not been reviewed by us in preparing this report. However it is clear that the scientific community holds it to be possible that lung cancer can be caused by agents other than cigarette smoke.

Magnitude of specificity cannot be asserted: the overall relative risk is not strong and is smaller than many of those associated with other potential risk factors.

Temporality

No study takes adequate account of this issue. Studies based on current exposure do not verify consistency of exposure. Those based on past exposure are subject to recall bias, and do not present a discussion of the anticipated lag time between exposure and response.

Biological Gradient

As discussed in detail above, no statistically significant exposure-response relationship distinct from an overall association has been documented either consistently in individual studies or with meta-analysis techniques. The possibility of a threshold response has not been explored systematically.

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Biological Plausibility

Biological plausibility rests on evaluations of the concentration and toxicity of constituents of ETS, the magnitude and duration of exposure, the actual exposure-response relationship if present, and consideration of histological types of lung cancer. All of these issues have been debated.

Experimental Evidence

There is no direct experimental evidence of the association between ETS and lung cancer in humans. Such experiments would be regarded as unethical in spite of the uncertainties of the epidemiological evidence.

Indirect experimental evidence, such as that reported by the EPA (1992, p.1-9), relies on the strength of the equivalence between the possible, putative or possible biological mechanisms, exposure levels and analogies between the experimental animals and humans.

Analogy

The immediate analogy is with active smoking, but as stated above it is made on the basis of a number of assumptions about which there is still some dispute. (See Section 1 of this Report.) Other carcinogens such as radiation and asbestos have been regarded as having no threshold dose but these have also been debated in the literature.

Conclusion:

Even under a liberal interpretation, only three of these tests might be considered to be passed: biological plausibility, coherence and analogy. All of the tests which require 'evidence', in the form of epidemiological, biological or experimental data, are failed or are at best equivocal.

It is our opinion, based on a thorough review of the available literature and the above evaluation, that although there is an apparent overall positive association between exposure to ETS and lung cancer in adults it is very weak especially in view of the potential for this association to be influenced by uncontrolled biases and confounders. Taking into account all of the above tests a causal relationship between exposure to ETS and lung cancer cannot be asserted at this time.

4.3. Heart Disease in Adults

Based on two cohort studies (Garland, 1985; Hirayama, 1981), the NH&MRC Report (1986, p.40) stated that "only limited evidence exists for any increased risk of cardiovascular disease in passive smokers" and that "it is essential to pursue this question further". This conclusion was broadly supported by the Reports of the United States Surgeon-General (1986) and the National Research Council (1986).

There are now 14 published epidemiological studies and more data from biological and experimental studies. It is the goal of this section to summarise these and to evaluate the overall support for a causal relationship between exposure to ETS and heart disease in adults.

4.3.1 Epidemiological Studies

Based on comprehensive searches of the literature we have been able to locate 14 epidemiological studies reporting on the relationship between exposure to ETS and heart disease. We are also aware of two other studies conducted in Australia (an Honours thesis by Liew (1992) and an unpublished PhD thesis by Sexton (1993)) which apparently report on the association between heart disease and ETS exposure, but we have been unable to locate these.

In the following discussion, we focus on the most recent published paper describing each study. For example, Hole et al. (1989) updates a report by Gillis et al. (1984); Hirayama (1984) updates his 1981 paper; Sandler (1990) updates both a 1989 report and Helsing (1988).

We have also considered a number of public reviews of these studies, including Reports by the Surgeon General (1986), NRC (1986), NH&MRC Report (1986), OSHA (1994). Other published reviews and discussion papers which have read include those by Wexler (1989, plus discussion), Beaglehole (1991, with reply by Seltzer), Glantz and Parmley (1991), Steenland (1992) and Taylor (1992).

A short summary of these epidemiological studies is provided in Table 4.3.1.1. More detailed reviews and tables are provided by Lee (1992) and the review articles.

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Of these studies, 7 are case control conducted in Australia (1), England (1), China (2), USA (2) and Italy (1). Seven are cohort studies conducted in USA (5), Scotland (1) and Japan (1).

Dobson's (1992) population-based case control study, conducted between 1988 and 1989 in NSW Australia, is arguably one of the best with respect to design, analysis and reporting. This population-based case control study, which considered exposure at both home and work, was designed specifically to study the association between heart disease and exposure to ETS. Controls were drawn from participants in a risk factor survey and the outcome was myocardial infarction or coronary death. This is the only study which provides details for an Australian population.

As discussed below, there are some fundamental differences between the studies with respect to design, definitions of exposure and outcome, study size, method of analysis, control of bias and confounding, and reported results. The consequent issues of study quality are addressed below.

Exposure to Spousal Smoking

All 14 studies listed in Table 4.3.1.1 provide some information on the relative risk of heart disease (variously defined) associated with exposure to ETS, as measured by spousal smoking.

As indicated in Table 4.3.1.1, although many of the studies have a large number of enrolled subjects, the number of cases may be quite small. This is reflected in the variety of reported relative risk estimates. While for females there are almost equal numbers of significant and nonsignificant estimates (at the 5% level), all but one of the five estimates for males are nonsignificant. Furthermore, an exposure response relationship is more often reported for females, whereas in only one study was a significant relationship reported for males and then only for death as an outcome.

Caution must be taken in interpreting the exposure response data: most studies consider only two exposure categories and quite different categorisations are used. Results are predominantly based on small numbers of cases in these categories. For example, Svendsen (1987) reports a significant relationship, but this is based on only one death in the 1-19 cigarettes exposure group.

Workplace Exposure

Relative risk of heart disease associated with workplace exposure is considered in four studies (Dobson et al., 1992; He et al., 1994; Lee et al., 1986; Svendsen et al., 1987).

While He et al. (1994) reports a significantly larger relative risk estimate associated with exposure at work, the other three papers find no such association; indeed Lee et al. (1986) and Dobson et al. (1992) report relative risk estimates which are less than unity, although apart from some subgroups in Lee's study these are not statistically significantly lowered.

In comparison with estimates for spousal exposure, He et al. (1994) report a larger relative risk from workplace exposure, whereas Lee and Dobson report comparably smaller estimates for both sexes. In He's study an additive effect of the two exposures is supported.

He et al. (1994) also report a significant exposure response relationship, based on four measures of exposure, but cautions that the trend is "not precise enough for risk assessment for unit dose of exposure". The other studies do not address this issue.

The relatively small numbers in the studies when divided into dosage categories leads to two problems. First, it is very difficult to establish a relationship even if one exists due to lack of power. Second, the effect of misclassification is amplified since a larger bias is observed with fewer misclassified subjects.

Previous Assessments

Lee et al. (1992) provides quite comprehensive summaries of the eight relevant studies available at the time; importantly, Dobson et al. (1992) is excluded. Based on this information, Lee concludes that there is no causal relationship between ETS exposure and heart disease. This is in contrast to the review by Steenland (1992), who on the basis of these studies, is sufficiently certain of a causal relationship that he can estimate annual attributable deaths. The EPA Report (1992) does not address the outcome heart disease.

Glantz and Parmley (1991) also provide an overview of the "evidence" that ETS is causally associated with heart disease and consequent calculations of attributable annual risk, and an overview of the various biological mechanisms which might cause this association. There is no critique of the weaknesses in the papers, and

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the authors appear to accept without demur the analysis of Wells (1988) and Kristensen (1989) that the link is causal. No new data or analysis is given to support this conclusion. Moreover, we disagree with some of their reported numbers, relative risks, and lists of factors for which adjustment was made. We also dispute the validity of the meta-analytic method used by Glantz and Parmley, although their overall relative risk is a reasonable estimate. As we discuss later, the biological papers are also problematical.

The Occupational Safety and Health Association (OSHA) Report (1994) also reviews these epidemiological studies and provides estimates of deaths attributable to occupational exposure in the USA. In an open review, Tweedie (1994) argues that the positive association asserted in the report is instead ambiguous and that the data related to workplace exposure to ETS are quite equivocal at this time. The OSHA Report asserts that five of the 11 studies give statistically significant elevated relative risks, and all are positive, whereas Tweedie believes that only 2 are significant, since Helsing et al. (1988) and Sandler et al. (1989) are actually the same study, and 3 are less than unity. Apart from the Chinese study of He et al. (1994), none of those that considered workplace smoking was unequivocal and one of them (Dobson et al., 1992) report a negative excess risk.

Meta-analysis

A meta-analysis of the overall association between exposure to ETS and heart disease has been published by Lee (1992). Apart from using only the eight studies then available, the fixed-effects method used in the analysis has since been found to be possibly too restrictive in its assumptions about the homogeneity of study estimates (see, for example, Mengersen, Tweedie & Biggerstaff, 1994).

Moreover, then (as now), there are overriding concerns about study quality and comparability that render any overall results from a simple model quite invalid. A meta-analysis in this case is useful for highlighting differences between studies, which include the following.

The study designs are not comparable. There is substantial difference in design between case control and cohort studies. A multiplicity of statistical methods have been employed, including proportional hazards models, Mantel-Haenszel estimates, logistic and multiple regression, Fisher's exact test and exact unadjusted confidence intervals.

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The studies do not measure the same outcome or exposure. Death and nonfatal events are both considered. Exposures from spouse, home, work, and combined estimates are variously reported. In previous meta-analyses these have simply been combined; this may render the results invalid if there is a true difference in relative risk between the various measures.

The study populations are not comparable. In the study of lung cancer, it has been observed that different relative risks may apply to different countries, indicating that important confounders may have been overlooked. This issue is discussed in more detail below. If one wishes to apply results to a particular population, it is valid to combine only studies measuring associations in equivalent populations.

The relative risk has not been established to be constant over time. There is substantial literature which asserts that mortality from heart disease is decreasing in Australia but the reasons for this are not yet well understood (Al-Roomi et al., 1989; Jackson & Beaglehole, 1987, among many others). If other risk factors or patterns of exposure have also changed, a summary relative risk estimate over all time periods may be invalid and, moreover, inapplicable to the current population (Breslow & Day, 1987, p.110).

Confounding factors are not adequately controlled. There are over 200 suggested risk factors for heart disease (Hopkins & Williams, 1981). Although many of these are linked, the most that any one study adjusts for is six, with different factors considered in the individual studies. Of primary concern is diet. Recent studies (Margetts & Jackson, 1993; Bolton-Smith et al., 1993; Midgette et al., 1993), including the epidemiological study by He et al. (1994), indicate that diet could be an important confounder.

The results may be subject to misclassification and bias. In addition, there are numerous examples of data dredging and hypothesis generating in the studies. These issues are discussed in more detail below.

Study Quality

As discussed in Section 2, it is important to evaluate reported results in light of study quality and it is imperative to take this into account in an assessment of causality.

Some concerns about the studies on heart disease are expressed below. Other issues have been raised in the above reviews..

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Definition of Exposure

In the studies, there is no consistent definition of exposure to ETS. Most studies define exposure in terms of spouse smoking, with the most common categorisation being as neversmoker, ex-smoker and current smoker, and quantification of current smoking in terms of number of cigarettes/day smoked by the spouse. Even within this definition, there are differences. Lee (1986) measures spouse smoking of manufactured cigarettes during the whole of the marriage. Helsing et al. (1988), Hole et al. (1989) and Dobson et al. (1992) define exposure in terms of cohabitants (not necessarily spouse) and even their definitions differ with respect to the time of exposure. He et al. (1994) defines passive smoking from the spouse as 'living with a smoking husband for over five years' and reports five different measures of exposure at work (Table 4.3.1.2).

The problems with the use of spouse smoking as a proxy for exposure to ETS, and consequent problems of misclassification and bias, have been discussed in Section 2.

Definition of Outcome

Although all studies measure heart disease as an outcome, three outcomes are in fact identified: death, nonfatal heart disease event, or both fatal and nonfatal disease. All of the cohort studies define death as the outcome measure, although some consider nonfatal outcomes as well (e.g. Svendsen et al. (1987) recorded heart attack or death). Lee et al. (1986) uses a final discharge diagnosis of disease; He (1994) considers non-fatal disease, and Dobson et al. (1992) and Svendsen et al. (1987) consider fatal or nonfatal coronary events. Based on the epidemiological data alone, it is difficult to evaluate the effect of having different outcome measures. If different risks were associated with death and event (not necessarily fatal), we might expect contrasting risks between the case control and cohort studies. This may well be confounded, however, with other design differences between the two study types, and different sources of bias and misclassification. In any event, comparison and combination of results from different studies should be conducted with caution.

The Surgeon General's Report "Health Consequences of Involuntary Smoking" (1986, p.106) states that "more detailed characterisation of exposure to ETS and specific types of CVD [cardiovascular disease] associated with this type of exposure are needed before an effect of involuntary smoking on the aetiology of CVD can be established." In our opinion this statement is still valid today.

Misclassification of Smoking Status

Misclassification of smoking status is one of the major problems in both the case control and cohort studies. Dobson et al. (1992, p.796) suggests that in their case control study, cases may underreport smoking and hence reduce the magnitude of estimates of risk, or may exaggerate smoking status as an explanation for the disease. Hence the observed risk could be spuriously raised or lowered.

Svendsen et al. (1987, p.793) made careful measurements at baseline and followup to rule out misclassification of active smokers as nonsmokers. They found no such differential misclassification.

In the studies of Hirayama (1981), Helsing et al. (1988) and Sandler et al. (1989), the smoking habits of both subjects and spouses were ascertained at the beginning of the study and were not updated during the study period. There is no information about the number of subjects or spouses who changed smoking habits during this period.

He et al. (1994) provide some information on retesting 35 hospital subjects (16 cases and 19 controls). He reports 75% to 95% agreement on 10 risk factors tests. Agreement on exposure was 74.3% (workplace) and 91.4% (home), but they "expect lower agreement for quantity of exposure". Unfortunately there is no information about whether there were any differential rates among exposed/unexposed or cases/controls. The authors comment that in this study there was no validation of exposure by cotinine. Yet conclusions are based largely on the quantity of exposure.

The effect of this type of misclassification has been studied by Lee (1986), Ahlborn and Uberla (1988) and Wald et al. (1986). Tweedie and Mengersen (1994) advocate a data-based sensitivity approach to assessing the effects of differential misclassification. Using a variety of published estimates of misclassification and marriage concordance, they demonstrate that relative risk estimates of up to 1.15 can be observed even if the true relative risk is unity. Since this is of the order of relative risks observed for heart disease, it is imperative that this source of bias be addressed in each individual study.

Misclassification of Exposure

The majority of the epidemiological studies record exposure through spousal or household smoking (most commonly cigarettes per day and pack-years). As

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discussed in Section 2, these measures are very poor indicators of true ETS exposure.

Indirect Reporting of Subject and Spouse Status

In Svendsen's (1987) study the spouse's smoking status was based on the husband's report. It is not clear in the Hirayama (1981) study whether the subjects or the spouses provided information about spousal smoking habits.

Lee et al. (1986, p.99) provide empirical evidence of misclassification of spouse smoking status using interviews of the spouse, the index patient, and both sources of information. Relative risks varied considerably, for example from 0.75 (based on index patient information) to 1.60 (based on spouse information) for females, but no consistent pattern was observed. Discrepancies were seen for 15% spouses with respect to smoking at some time during the marriage and 3% with respect of smoking during the year of hospital interview.

Misclassification of Outcome

Death certificates were used in Hirayama's (1981) and the Helsing et al. (1987) studies; this is an acknowledged source of potential misclassification. Some published estimates of misclassification due to reliance on death certificate information for lung cancer are 8% (Garfinkel, 1980, p.1171), 10% (Uberla, 1987, p.424). Wexler (1989) and Stehbens (1990) discuss this problem in the context of heart disease; misclassification rates of over 25% have been reported. Lee et al. (1986) uses hospital records in the ascertainment of cases. In his (ETS/lung cancer) study, Garfinkel (1981) found a strong association based on hospital records and a much weaker association after partially correcting for it.

He et al. (1994) report that 26 out of 84 patients originally diagnosed with cardiovascular disease were subsequently confirmed by coronary arteriography to be normal. This group was reportedly not different from other controls with respect to proportion exposed, but they were indeed different from cases. Hence if they were included as cases, the true relative risk would have been underestimated. Yet even with this very good assessment of the status of the controls the relative risks were still not significant.

Confounding and other Risk Factors

Consideration of the entry criteria for each study indicates the sometimes poor and certainly inconsistent (between studies) control of possible confounding

factors. These include age, sex, degree of exposure, health (blood pressure, cholesterol, obesity, previous history of heart disease, alcohol intake) and lifestyle (socioeconomic status, education, housing quality).

As indicated in Table 4.3.1.2, there is inconsistent control of these possible confounding factors. Furthermore, the risks after adjustment for the factors are not consistently raised or lowered from the crude risk. For example, Svendsen (1987) found no difference after adjustment, whereas adjustment made a very large difference to the risks in Helsing's (1988) study.

While all studies adjust for age, there remains concern that this adjustment is inadequate. For example, the age of the study group differs among studies: Sandler sets a minimum age of 25 years; Garland et al. (1985) consider only subjects aged 50-79 years. Despite this, there is no consistent pattern of risks for studies of similar age groups. Furthermore, adjustment for age is not consistent among studies. For example, Hirayama (1981) does not use the standard cohort analysis methods (e.g. proportional hazards models, multiple/logistic regression) and standardises by age of spouse instead of age of subject. Unfortunately we cannot assess the effect of this using the available data.

Lee (1991, p.24) argues that "knowing the age distribution of a group of cases and controls is similar does not necessarily imply that the age distribution of cases and controls who never smoked is comparable, and it is the latter requirement that is needed for proper adjustment for age."

Roe (cf. Wexler, 1989, p.164) argues that measures like cholesterol or socioeconomic status are not sufficient indicators of lifestyle. The large differences between observed risks for men and women is not adequately explained in any of the papers. Less well acknowledged confounding factors may also materially influence results.

One such factor is *previous heart disease*, studied only by Dobson (1991, p. 796), who found it to be a significant confounder for smoking and the risk of heart attack or coronary death. Other factors which have been found to be possible risk factors for related diseases (e.g. in the lung cancer studies, nutrition (Hirayama, 1984), asbestos (Humble et al., 1987)) were not considered in the heart disease studies.

Diet is another important confounder which has been quite widely documented (He et al., 1994; Hirayama, 1984; Akiba et al., 1986). A substantial difference in dietary habits among active smokers compared with nonsmokers has been

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reported (Midgette et al., 1993; Margetts & Jackson, 1993; Bolton-Smith et al., 1993; Lee, 1992). Among nonsmokers, relative risks have been observed for heart disease associated with various dietary factors which are at least as high as that observed with ETS exposure; if there is indeed a differential effect between those exposed and unexposed, or between cases and controls, such a confounder could easily explain the ETS association. As illustration, although He et al. (1994) reports a crude relative risk estimate of 2.12-2.45 (depending on source), after adjusting for cholesterol (among other factors) the reported values in Table 4.3.1.2 are not significant.

In light of these concerns, while it is obviously important to control for major confounding factors, the adjusted risks reported in the papers should be treated with caution.

Data Dredging

There are a number of data dredging examples in these studies. Most of the analyses were based on subgroups of larger studies. For at least three analyses (Svendsen et al., 1987; Hirayama, 1981; Lee et al., 1986), data on ETS was obtained only in the latter part of the larger studies. In some papers, the lag between finalisation of the study and publication of the results is noticeable. For example, the Garland et al. (1985) study finished in 1973.

As a consequences of this, results may be hypothesis generating; that is, they should not be used to test hypotheses that were not specified prior to the start of the study. Furthermore, the analysis is more subject to selection bias since the study populations were already established.

In individual studies, specific subgroups are identified separately or combined, giving rise to potential for internal data dredging. If these categorisations were decided in advance, this is a useful way of avoiding confounding; if not, it may be data dredging. Some illustrations of this are given below.

Garland presents results for ex-smokers and current smokers, then uses a combined risk by merging the two exposure categories. This avoids the anomaly of most (15/17) deaths occurring in the ex-smoker exposure category, and provides more power for an estimate of combined risk. Not only is the interpretation of this risk difficult, but it may be an artefact of data dredging.

Exposure response relationships are evaluated using arbitrary and inconsistent dosage levels. Even using the same measurement as cigarettes/day, dosages

range from 1-19/20+ (Svendsen), to <10, 10-20, 20+ (Humble) to 1-14, 15+ (Hole). 'Scores' used by Helsing and Lee are also seemingly arbitrarily combined. Given the small numbers of cases in these studies, changes in dosage levels may result in quite different interpretations of a dose response relationship.

Hirayama controls for age of husband instead of age of subject. If data are standardised for age of subject, the association reported by Hirayama disappears (Lee, 1992).

Risks published in Hirayama's 1981 paper are standardised for age and occupation, whereas standardisation in the 1984 paper was based only on age. Hence the large discrepancy between the reported risks in the two papers is either due to a very large increase in incidence of heart disease among exposed subjects (a risk of about 5 in the latter part of the study which Lee (1992) argues is "implausible" when compared with the first 14 years, or with active smoking risks) or it is a result of data dredging.

Day (1985, p.22) supports the argument that the search for subgroups which achieve nominal significance "tends to generate spurious positive results". He cautions that such positive results for subgroups should be consistent across studies; this is not apparent in the set of ETS/heart disease studies. Day also comments that a real effect may be masked if the data are subdivided in an effort to control confounding factors.

Nonresponse and loss to followup

Various authors provide percentages of nonrespondents: Hole, 20%; Humble, 8%; Helsing, 2%; Gillis, 20%; Garland, 18%; Dobson, 20-37%; He (1994) 20%.

Three authors provide percentages of subjects lost to followup: Svendsen, 0%; Garland, 0.4%; Sandler/Helsing, 85% for males and 51% for females.

Criqui et al. (1978) are reported by Dobson (1991, p.795) to have examined differences between respondents and nonrespondents in a population based cardiovascular disease study; their conclusion is that 'people who respond to risk factor surveys are less likely than nonrespondents to be smokers'. This is supported by Dobson, who compares nonrespondents and respondents with respect to smoking prevalence rates and concludes that nonresponse among control subjects can lead to underestimation of prevalence of smoking and consequently an overestimation of relative risk.

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Representativeness

In addition to problems of nonresponse and followup, some of the cohort study populations appear to be unrepresentative of the general population. Garland uses a cohort of women in a Californian retirement community; Svendsen analyses results for men at high risk of heart disease; Hirayama studies an agriculturally based cohort of women in 29 nonrandomly selected centres. A further instance of nonrepresentativeness is given by Sandler/Helsing, who only records as cases members of the cohort who die within the country. This may be a source of bias but there are no data to quantify this and Helsing does not discuss it. Similarly, the case control studies are quite different. Lee's study is matched and hospital-based, whereas Dobson's is a population based study.

One obvious misrepresentation due to failure to control for a confounding factor is found in Hirayama's study. As discussed above, the age distribution of the study cohort was not representative of the Japanese population (Ahlborn & Uberla, 1988). After appropriate age-adjustment in Tweedie's (1991) method, there is no significantly increased relative risk for the heavily exposed group.

Prejudgement Bias

This type of bias applies when a study is conducted using an hypothesis other than one of no association. For example, Garland tests the hypothesis that there is an increased risk of death from ischaemic heart disease associated with exposure to spouse smoking, and uses one-sided significance tests accordingly. Similarly, Hirayama uses one-sided significance tests.

There are two problems arising from this. The first is that the possibility of a negative association is excluded. The second is that adjustment for confounding factors may be influenced by the hypothesis. This is argued in more detail by Weiss (cf. Wexler, pp.154-5).

Publication Bias

This is discussed in Section 2 and may be relevant when evaluating the present association.

Recall Bias

As discussed in Section 2, cases may recall such exposure more readily than controls. If this is not taken into account, it may lead to spuriously inflated observed relative risks.

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Broken Heart Syndrome

Garland et al. (1985, p.649) examined whether widowhood results in increased risk of death because of the so-called 'broken heart syndrome', but found that it was unrelated to the excess mortality.

Attributable Risk

Estimates of attributable risk have been most recently made in the OSHA Report (1994). A "lifetime occupational risk" of heart disease for exposure to workplace ETS is calculated to be 7-16 per 1000 nonsmoking workers.

Tweedie (1994), in a critique of the OSHA Report, refutes these estimates. He claims that "the logic underlying them is faulty...and the data used in deriving them are not appropriate, leading at the very least to an exaggeration of the real situation" (p3). From Australian data and the National Heart Foundation summaries of population attributable fractions, Tweedie finds that less than 4% of Australians die from heart disease between the ages of 20 and 65, with 65-80% of these attributed to active smoking (15%), high blood cholesterol (30-40%) and high blood pressure (20-25%). It is difficult to reconcile these figures with OSHA's prediction that 33% of deaths before 65 are due to heart disease, and that over 1/3 of these deaths among nonsmoking males is caused by workplace exposure to ETS. Moreover, taking incidence rates proposed by Steenland (1992), Tweedie finds that the effective annual risk in the lower age group is totally negligible and that there is an effect only 1/3 that used by OSHA which is over only the latter 20 year period.

One of the present authors (KM) has reviewed this argument in detail and supports this criticism.

This illustrates the fact that attributable risk estimates are only as sound as the estimates and models on which they are based. It is imperative that, if they are used at all, they are accompanied by substantial sensitivity analyses which indicate the range of estimates that could be generated under alternative supportable assumptions. In particular, it is our belief that the conclusions and extrapolations made in the OSHA report should be treated with very considerable caution.

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4.3.2 BIOCHEMICAL ANALYSES

Cotinine, a metabolite of nicotine, is reportedly a common and effective marker of tobacco smoke intake for passive smoke dosimetry (NRC Report, 1986, p.226; Darby & Pike, 1988; Repace & Lowry, 1990).

Other biochemical markers have also been used. Dobson (1991) identified fibrinogen as a marker for exposure to ETS. The association between fibrinogen and passive smoking was positive but not statistically significant.

Tweedie and Mengersen (1992) provide a reconciliation of the biochemical and epidemiological results for exposure to ETS and lung cancer. Adopting their assumptions we may use their argument to assess the overall relative risk for heart disease, from comparable estimates for active smoking. The Surgeon General's Report (1986) quotes relative risks for the latter from 1.36 to 2.08, depending on country and age group, for coronary heart disease; Dobson (1991) reports adjusted relative risks of 4.70 for women and 2.71 for men, for myocardial infarction or coronary death. If we use a relative risk of 4 for heart disease associated with active smoking, then their calculations reveal that, due to possible misclassification of active smokers, an observed relative risk for heart disease associated with exposure to ETS should be reduced by 0.08.

4.3.3 BIOLOGICAL STUDIES

On the basis of epidemiological, physiological and biochemical evidence Glantz and Parmley (1991, p.10) conclude that ETS causes heart disease. In addition to the epidemiological studies Glantz and Parmley review three lines of biological evidence: 1) effect of ETS on exercise tolerance in healthy persons and in those suffering from preexisting CHD; 2) effect of ETS, or components of ETS, on platelet aggregation and endothelium; 3) effect of carcinogens in ETS on atherogenesis (in line with the hypothesis that lesions are equivalent to tumours).

In our opinion the biological papers quoted by Glantz and Parmley as supporting their claim have numerous weaknesses and flaws and do not support a causal relationship. Even the associative evidence is weak.

Reduced Exercise Tolerance

There is evidence that ETS may significantly increase ischaemic stress in people with *preexisting* CHD (Khalfen & Klochkov, 1987; Aronow, 1978). Healthy

persons, however, are either not affected (Khalfen & Klochkov, 1987) or are only marginally affected (McMurray et al., 1985). Glantz and Parmley emphasise the findings of McMurray et al. yet an examination of the data reveals that the actual differences are very small and the significance only marginal. Figures 1 and 3 illustrate how small the differences are in reality.

In support of the exercise data Glantz and Parmley quote Moskowitz et al. (1990) who investigated the correlation between passive smoking in children (whose parents smoked) and lipoprotein and oxygen transport alteration, and Gvozdjakova et al. (1984) who investigated the effects of passive smoke on the energetic processes of myocardial mitochondria. With respect to the former paper the authors did find an association between thiocyanate, as a marker for ETS exposure, and 2 3 diphosphoglycerate, as a marker for oxygen stress, but only for maternal not paternal smoking. Several confounders, including thiocyanate from dietary sources, and genetic variability in DPG, could affect the results. The differences between "non-smoking twins" and "smoking twins" are also very small with increases in DPG averaging only about 6%. Thus the strong inference in the Glantz and Parmley paper that the data are of great importance is not warranted.

With respect to the paper by Gvozdjakova et al. this too is given prominence yet the model used, exposure of rabbits to ETS, is not very different from active smoking (carboxyhaemoglobin levels of 6.68% which is about the same as in humans after active smoking - 5.95%). To extrapolate the results to passive smoking and to chronic effects is not warranted.

Glantz and Parmley then report on the effect of CO on myocardial damage (Kjendsen et al., 1974; Thomsen & Kjeldsen, 1974; Lough, 1978). The data are not convincing and importantly damage only occurs at higher levels of exposure (200-300ppm) and then not in all animals. It is notable that there were no changes at a lower level of 50ppm. In the Thomsen and Kjeldsen paper there is also evidence of recovery from damage induced by 180ppm over 48 hours. Thus any effects may be very short term and the cells may adapt. The biological plausibility is therefore questionable on several counts and the relationship to ETS and atherogenesis is at best tenuous. A number of studies have reported that CO is not atherogenic (reviewed by Smith & Steichen, 1993).

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